

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

1-5. (Cancelled)

6. (Withdrawn) A natural humanized antibody obtained by a method of preparation according to claim 1.

7. (Withdrawn) A natural human antibody containing CDR derived from a first animal species and the FR derived from a second animal species, characterized in that said FR comprises an amino acid sequence having amino acid residue different from the FR used for CDR-grafting by one or a plurality of amino acid residues and that said FR has been replaced with an FR derived from a second animal species and having the same amino acid residues as said different residue at the same positions.

8. (Withdrawn) The natural humanized antibody according to claim 7, wherein the first animal species is rat and the second animal species is human.

9. (Withdrawn) DNA encoding the natural humanized antibody according to claim 6.

10. (Withdrawn) An expression vector comprising the DNA according to claim 9.

11. (Withdrawn) A host comprising the DNA according to claim 10.

12. (Withdrawn) A method of preparing a natural humanized antibody, which comprises culturing the cells into which an expression vector comprising the DNA according to claim 9 has been introduced and recovering the desired natural humanized antibody from the culture of said cells.

13. (Withdrawn) A pharmaceutical composition comprising a natural humanized antibody.

14. (Currently Amended) A method for preparing a humanized antibody, wherein a framework region ("FR") in the humanized antibody is a FR naturally occurring in human antibodies, comprising the steps of:

(1) obtaining a ~~primary design~~ humanized antibody ~~which is humanized by a grafting of, wherein the humanized antibody has:~~

i) a complementary determining region ("CDR") of a first animal species;
~~and and which is substituted in one or more amino acid residues of the FR with artificial amino acids that do not occur in nature~~

ii) FRs of a second animal species, wherein one or more amino acid residues in one or more of the FRs have been substituted to retain antigen binding ability, with corresponding amino acid residues in FRs of the first animal species, and wherein said second animal species is human;

(2) conducting a homology search using a database of amino acid sequence of FRs naturally occurring in human antibodies ("natural FRs") in comparison with ~~a FR sequence of the primary design antibody~~ the amino acid sequence of the FR in which amino acid residues have been substituted in step (1), of the humanized antibody obtained in step (1);

(3) preparing a list of amino acid sequences of the natural FRs having the same as or a high homology with the FR sequence in the primary design antibody amino acid sequence of the FR, in which amino acid residues have been substituted in step (1), of the humanized antibody obtained in step (1),

(4) selecting, from the list of step (3), a natural FR which ~~contains a sequence that matches amino acids sequences substituted in step (1)~~ has

i) at corresponding positions the same amino acid residues as the amino acid residues introduced by the substitution in step (1); and

ii) comprises an amino acid sequence that is the same as or has a high homology with the FR sequence of the primary design antibody humanized antibody obtained in step (1);

(5) ~~if the FR sequence of the primary design antibody~~ if the amino acid sequence of the FR, in which amino acid residues have been substituted in step (1), of the humanized antibody obtained in step (1) has one or more amino acids acid residues that are different from amino acids acid residues at corresponding positions of the natural FR selected in step (4),

~~replacing~~ replace said different amino acid residues in the FR sequence of the ~~primary design antibody~~ humanized antibody obtained in step (1) with corresponding amino ~~acids~~ acid residues in the natural FR;

- (6) constructing an expression vector expressing an amino acid sequence of the antibody obtained via steps (1) to (5);
- (7) culturing cells comprising an expression vector constructed in step (6); and
- (8) recovering the humanized antibody comprising the natural FR from the culture.

15. (New) The method according to claim 14, wherein the first animal species is a non-human mammal.

16. (New) The method according to claim 14, wherein high homology comprises a homology of at least 80%.

17. (New) The method according to claim 14, wherein the searched sequence is the same as the target sequence.

18. (New) The method according to claim 15, wherein the non-human mammal is selected from a mouse, rat, hamster, rabbit and monkey.

19. (New) The method according to claim 14, wherein all natural FRs belong to the same subgroup.

20. (New) The method according to claim 14, wherein the number of the substituted amino acid residues of the FR in step (1) is from one to ten.

21. (New) The method according to claim 14, wherein the number of the different amino acid residues in the FR in step (5) is from one to ten.

22. (New) The method according to claim 14, wherein the substituted amino acid residues in the FR in step (1) comprise an amino acid residue selected from amino acid residues responsible

for canonical structure of the antibody, amino acid residues involved in the maintenance of the structure of CDRs, and the amino acid residues that directly interact with an antigen.

23. (New) The method according to claim 20, wherein the substituted amino acid residues in the FR in step (1) comprise an amino acid residue selected from an amino acid residue at position 71 of the heavy chain or at position 94 of the heavy chain.